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EXAMINER	
BAUGHMAN, MOLLY E	
ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/585,682	TETZNER ET AL.	
	Examiner	Art Unit	
	Molly E. Baughman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *21-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☒ Claim(s) *12,17 and 18* is/are objected to.

8)☒ Claim(s) *1-23* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/10/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-20, drawn to a method for the analysis of cytosine methylation.

Group II, claim(s) 21-23, drawn to a kit comprising a probe, a repair enzyme, a polymerase, and additional reagents necessary for PCR.

2. The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical feature of Group I, claim 1: "*A method for the analysis of cytosine methylation, characterized in that: a) the DNA to be investigated is chemically or enzymatically converted so that 5- methylcytosine remains unchanged, while unmethylated cytosine is converted to uracil or to another base which differs from cytosine in its base pairing behavior, b) the converted DNA is hybridized with oligonucleotides, whereby the DNA of one methylation status forms hybrids with erroneous base pairings, while the DNA of the other methylation status forms hybrids without erroneous base pairings or does not form hybrids, c) one strand of the erroneously paired hybrids is enzymatically cleaved, d) the uncleaved DNA or the cleaved fragments are detected, e) the methylation status of the investigated DNA is concluded from the detection signal generated in step d),*" does not provide contribution over the prior art (see Berlin (AU 200018565 B2), entire document, specifically, pg.6-8, 12-14).

3. During a telephone conversation with Edward Kriegsman on 10/31/08 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-20. Affirmation of this election must be made by applicant in replying to this

Office action. Claims 21-23 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

4. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

5. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP

§ 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

6. Claims 1-20 are currently under examination.

Information Disclosure Statement

a. The information disclosure statement (IDS) submitted on 7/10/2006 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. However, some citations have been either modified, or lined through for the following reasons:

a. The documents under "Foreign Patent Documents," are not being considered as they are in a foreign language.

Claim Objections

7. Claim 12 is objected to because of the following informalities: "a DNA repair enzyme are utilized," is not proper grammar. Appropriate correction is required.

8. Claims 17-18 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claims recite an intended use of the method of claim 1, without reciting any positive active steps which would further limit the method.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

b. Claims 1-20 are confusing because it cannot be determined what is encompassed by the term, “characterized in that.” The scope of the phrase is unclear, and it is suggested to use conventional U.S. claim language, such as “comprising,” or “wherein.”

c. Claims 1-20 are confusing because claims 1, 4, 5, 7, 9-10, 12, and 14-16 do not recite any active steps. For instance, “is hybridized,” is not considered a positive, active step. While minute details are not required in method claims, at least the basic steps must be recited in a positive, active fashion. See Ex parte Erlich, 3 USPQ2d, p. 1011 (Bd. Pat. App. Int. 1986).

d. Claim 5-7 are confusing because it cannot be determined what is encompassed by "background DNA," first cited in claim 5, and also appears in

numerous dependent claims. It is unclear from the claim and specification what is encompassed by this type of DNA. Furthermore, not providing such description also renders the invention unclear, so it is suggested to provide further clarification.

e. Claim 5 recites the limitation "the background DNA." There is insufficient antecedent basis for this limitation in the claim.

f. Claim 7 is confusing because it cannot be determined what is encompassed by “the oligonucleotides utilized in step b) are simultaneously utilized as primers or probes in a later amplification step.” The phrase is unclear as written, since first, it is confusing how the oligonucleotides are simultaneously utilized, and second it is unclear how they can be *simultaneously* utilized in a *later* amplification step. Clarification is required.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1-6, 12, and 17-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Berlin (AU 200018565 B2, published June 2000).

Regarding claim 1, Berlin teaches a method for the analysis of cytosine methylation, characterized in that:

a) the DNA to be investigated is chemically or enzymatically converted so that 5-methylcytosine remains unchanged, while unmethylated cytosine is converted to uracil or to another base which differs from cytosine in its base pairing behavior (see pg.6, pg.7, second full paragraph; bottom half; pg.11, last paragraph) ,

b) the converted DNA is hybridized with oligonucleotides, whereby the DNA of one methylation status forms hybrids with erroneous base pairings, while the DNA of the other methylation status forms hybrids without erroneous base pairings or does not form hybrids (see pg6, bottom half; pg.8, first half; pg.12, last paragraph),

c) one strand of the erroneously paired hybrids is enzymatically cleaved (see pg.6 – step c); pg.10, first half; gp.13, second to last paragraph).

d) the uncleaved DNA or the cleaved fragments are detected (pg.7 – step e); pg.8, bottom half; pg.10, bottom half; pg.14, top half),

e) the methylation status of the investigated DNA is concluded from the detection signal generated in step d) (see pg.7 – step e); pg.8, bottom half; pg.10, bottom half; pg.14, top half and examples).

Regarding claims 2-3, Berlin teaches the method further characterized in that in step b), the DNA of one methylation status forms hybrids with erroneous base pairings, while the DNA of the other methylation status forms hybrids without erroneous base pairings, or does not form hybrids (see pg.8, first half; pg.12, second half – which discusses erroneous base pairings in the heteroduplexes formed, the reaction also inherently includes situations where some hybrids do not form).

Regarding claim 4, Berlin teaches a a method for the analysis of cytosine methylation, characterized in that:

a) the DNA to be investigated is chemically or enzymatically converted so that 5-methylcytosine remains unchanged, while unmethylated cytosine is converted to uracil or to another base which differs from cytosine in its base pairing behavior,

b) the converted DNA is hybridized to oligonucleotides, whereby the DNA to be detected forms hybrids with erroneous base pairings,

c) the oligonucleotide strand of the erroneously paired hybrids is enzymatically cleaved, d) the cleaved oligonucleotide fragments are detected,

e) the methylation status of the investigated DNA is concluded from the detection signal generated in step d) (see claim 1 for Berlin's teachings).

Regarding claim 5, Berlin teaches a method for the analysis of cytosine methylation, characterized in that:

a) the DNA to be investigated is chemically or enzymatically converted so that 5-methylcytosine remains unchanged, while unmethylated cytosine is converted to uracil or to another base which differs from cytosine in its base pairing behavior,

b) the converted DNA is hybridized to oligonucleotides, whereby the background DNA forms hybrids with erroneous base pairings,

c) the DNA strand of the erroneously paired hybrids is enzymatically cleaved,

d) the uncleaved DNA is detected,

e) the methylation status of the investigated DNA is concluded from the detection signal generated in step d) (See claim 1 for Berlin's teachings, and also pg.8, where hybrids form duplexes in unchanged DNA, which is subjected to cleavage in the invention (and will not be cleaved), and then detected by mass spectrometry by size).

Regarding claim 6, Berlin teaches the method further characterized in that the background DNA forms several erroneous base pairings with the oligonucleotides (see pg.12, second half – which discusses erroneous base pairings in the heteroduplexes formed).

Regarding claim 12, Berlin teaches the method further characterized in that in step c) a DNA repair enzyme are utilized (see pg.6 – step c); pg.10, first half; gp.13, second to last paragraph, Muts).

It is noted that due to the indefiniteness of claims 17-18, it cannot be determined how the instant invention differs from the prior art.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Berlin (AU 200018565 B2, published June 2000).

Berlin teaches the method of claim 1, however are silent to whether steps c) to e) are conducted simultaneously, however, MPEP 2144.04 IV C states that the "selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results" (*In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946)).

16. Claims 7-10 and 19-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Berlin (AU 200018565 B2, published June 2000) in view of Herman et al (US 6,265,171).

The teachings of Berlin are discussed above. Berlin does not discuss the method where the detection is performed by nucleic acid amplification. She is also silent to the source of the DNA with respect to body fluids.

However, Herman teaches a method of detecting cytosine methylation patterns by converting nonmethylated cytosines to uracil, then, amplifying and detecting the converted DNA using methylation specific primers (see abstract and col.3, col.4, lines 29-48; col.5-6; Fig.2A-E; and col.9, lines 51-67). Herman also teaches samples

obtained from serum, plasma, urine, sputum or other body fluids of an individual (see col.7, lines 59-62).

One of ordinary skill in the art would have been motivated to modify the method of Berlin to detect using methylation specific amplification, as well as use samples obtained from body fluids because it was conventional in the art at the time of the invention to use methylation specific amplification to detect cytosine methylation patterns from body fluid samples, as demonstrated by Herman et al. Since Berlin demonstrates the benefits of detecting methylated cytosines following conversion of DNA, and enzymatic cleavage in human samples, and Herman et al demonstrate that it was conventional in the art at the time of the invention to detect via methylation specific primer pairs in amplification of DNA from body fluid samples, it would have been obvious to one skilled in the art to substitute one detection method for the other to achieve the predictable result of detecting methylated cytosines in DNA following DNA conversion in body fluid samples.

17. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Berlin (AU 200018565 B2, published June 2000) in view of Gitan et al., "Methylation-Specific Oligonucleotide Microarray: A New Potential for High-Throughput Methylation Analysis," Genome Research, 2002, Vol.12, No.1, pp.158-164.

The teachings of Berlin are discussed above. Berlin does not discuss the method where the detection in step d) is made by means of a microarray.

However, the use of microarrays to detect methylated cytosines in DNA was well known in the art at the time of the invention (see Gitan, abstract). Therefore, one of skill

in the art would have been motivated to use a microarray during the detection step since Gitan demonstrates the benefits of using microarrays to detect methylation patterns in DNA. Since Berlin demonstrates the benefits of detecting methylated cytosines following conversion of DNA, and Gitan et al. demonstrate that it was conventional in the art at the time of the invention to detect methylation patterns via microarrays, it would have been obvious to one skilled in the art to substitute one detection method for the other to achieve the predictable result of detecting methylated cytosines in DNA following DNA conversion.

18. Claims 13-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Berlin (AU 200018565 B2, published June 2000) in view of Bazar et al, "Mutation Identification DNA analysis system (MIDAS) for detection of known mutations," Electrophoresis, 1999, Vol.20, pp.1141-1148 (of record).

The teachings of Berlin are discussed above. Although Berlin discusses using a DNA repair enzyme, MutS, to recognize and cleave mismatched base pairs in pretreated DNA, she does not discuss the DNA repair enzyme being Mut Y, Mug protein, DNA glycosylase, or TDG enzyme [claim 13], or a heat-stable enzyme [claim 14], or specifically, TDG enzyme [claim 15].

However, the use of DNA repair enzymes to detect mismatched or erroneously base paired DNA via detection of fragments cleaved by such enzymes was well-known in the art at the time of the invention. Bazar et al. demonstrate using DNA glycosylase

and thermostable TDG enzyme in such reactions (see abstract, pg.1142, "Thermophilic MIDAS reaction;" Figure 1; pg.1144 "Detection of A/A mismatch with E. Coli Endo V").

One of ordinary skill in the art would have been motivated to modify the method of Berlin to different DNA repair enzymes, such as Mut Y, Mug protein, DNA glycosylase, or thermostable TDG enzyme because it was conventional in the art at the time of the invention to use such repair enzymes in reactions to recognize and cleave erroneously base paired DNA in detection of, erroneously base paired DNA, as demonstrated by Bazar et al. Since Berlin demonstrates the benefits of detecting methylated cytosines using a DNA repair enzyme, and Bazar et al demonstrate that it was conventional in the art at the time of the invention to use DNA repair enzymes, DNA glycosylase, and thermostable TDG enzyme in erroneously base paired DNA detection reactions, it would have been obvious to one skilled in the art to substitute one DNA repair enzyme for the other to achieve the predictable result of using DNA repair enzymes to detect methylated cytosines in DNA following chemical conversion of DNA.

Summary

19. No claims are free of the prior art.

20. McCutchen-Maloney (US 6,340,566) is noted as a reference of interest.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Molly E. Baughman whose telephone number is (571)272-4434. The examiner can normally be reached on Monday-Friday 8-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kenneth R Horlick/
Primary Examiner, Art Unit 1637

/Molly E Baughman/
Examiner, Art Unit 1637